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# A Community Prevalence Study of Antibodies to Hepatitis A and E in Inner-City London

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The seroprevalence of antibodies to hepatitis E virus (HEV) and hepatitis A virus (HAV) was determined in a community-based sample in inner-city London where socioeconomic conditions were expected to result in a high prevalence of antibodies to HAV, and in which the presence of immigrants from the developing world pose a risk of imported infection of both HAV and HEV. The seroprevalence of anti-HAV was 45.1% in UK born subjects and 69.7% in non-UK born subjects and each group showed differing patterns of age-specific seroprevalence. The seroprevalence rates of anti-HEV was 3.9% in UK born subjects and 8.8% in non-UK born subjects. The age-specific seroprevalence of the UK born group is suggestive of a cohort effect. The data suggest a low circulation of HEV in inner-city London, remaining uncommon relative to HAV.



**KEY WORDS:** community study, anti-HAV, anti-HEV

## INTRODUCTION

Hepatitis A virus (HAV) and hepatitis E virus (HEV) are responsible for the majority of cases of non-parenterally transmitted hepatitis worldwide. Both viruses commonly cause an acute self-limiting illness with no chronic sequelae, but which may in a minority of cases result in acute liver failure with a high mortality. They have some common features in that both are implicated as the cause of endemic and epidemic infections and are commonly spread by faecal contamination of drinking water or foodstuffs. Coexistence of both viruses has been shown in serological studies in India [Arankalle et al., 1995], Taiwan [Lee et al., 1994] and Central Africa [Pawlotsky, 1995]. HAV is endemic in the United Kingdom (UK) and 2,000 to 7,000 cases are confirmed and reported annually [Gay et al., 1994; Heptonstall, personal communication]. There is limited data on the epidemiology of HEV in Western Europe; studies on blood donors have revealed a low seroprevalence of antibodies to HEV (anti-HEV) in Germany [Wang et al., 1993] and the Netherlands [Zaaijer et al., 1993] though HEV has been implicated as a cause of both imported and locally acquired sporadic hepatitis and of fulminant hepatic failure in recent reports, including disease acquired in the UK [Zaaijer et al., 1993; Sallie et al., 1994].

A community-based survey in London is described for anti-HEV and anti-HAV. The sample is from an inner-city area, previously studied to establish the prevalence of hepatitis B (HBV) and C (HCV), and with high rates of unemployment, overcrowding and poor housing. All these factors have been associated with high rates of HAV infection [Melnick, 1995; Dubois et al., 1992], and we wished to investigate whether this would also be associated with high rates of HEV infection. The possible role of imported infection from the large numbers of immigrants from areas of high endemicity present in the area sampled was also of interest.

## SUBJECTS AND METHODS

### Subjects

The full details of sample collection for this study were published in the initial study of HBV and HCV [King et al., 1991]. Briefly, 1,002 sera were collected from 691 female and 311 male (mean age 41 ± 16 SD) patients attending general practitioners in 12 practices in the Camberwell health district for reasons unrelated to hepatitis in 1988–89. Each patient attending the practice during a 2-month period was given printed information explaining the survey and invited to participate. Approximately 10–20% of those attending agreed to do so. Testing for markers of hepatitis B infection was performed with informed consent, and testing for hepatitis A, C and E was performed on an anonymous basis. The study was carried out with the approval of the ethical committee of Kings Healthcare NHS Trust.

At protocol interviews basic demographic information regarding age, sex, country of birth, parents' country of birth and the age at emigration to the UK was recorded. Subjects were specifically questioned with regard to his-

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TABLE I. Age and Sex Profiles of Samples

| | Age groups (years) | | | | | | | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 15–44 | | 45–64 | | 65–74 | | >75 | | | |
| | N | (%) | N | (%) | N | (%) | N | (%) | N | (%) |
| Male | | | | | | | | | | |
| Attendees | 235 | (59.9) | 100 | (25.5) | 43 | (11.0) | 14 | (3.6) | 392 | (100) |
| GP sample | 78 | (54.5) | 49 | (34.3) | 12 | (8.4) | 4 | (2.8) | 143 | (100) |
| Whole sample | 170 | (54.7) | 106 | (34.1) | 27 | (8.6) | 8 | (2.6) | 311 | (100) |
| Female | | | | | | | | | | |
| Attendees | 443 | (67.5) | 119 | (18.2) | 57 | (8.7) | 37 | (5.6) | 656 | (100) |
| GP sample | 220 | (68.3) | 85 | (26.4) | 15 | (4.7) | 2 | (0.6) | 322 | (100) |
| Whole sample | 426 | (62.4) | 202 | (29.6) | 41 | (6.0) | 14 | (2.0) | 683 | (100) |

Attendees: data from GP attendance diaries.
GP sample: subjects in sample who attended GP practices where diaries were studied.

TABLE II. Ethnic Origins and anti-HAV and -HEV Seropositivity of Subjects

| | | No. (%) Positive | | | |
|---|---|---|---|---|---|
| Birthplace | Number | IgG anti-HAV | | IgG anti-HEV | |
| UK | 710 | 320 | (45.1) | 28 | (3.9) |
| Eire | 27 | 20 | (74.1) | 1 | (3.7) |
| Africa | 44 | 31 | (70.5) | 3 | (6.8) |
| Bangladesh/ Pakistan | 26 | 19 | (73.1) | 6 | (23.1) |
| India | 13 | 11 | (84.6) | 1 | (7.7) |
| Southeast Asia | 16 | 9 | (56.3) | 3 | (18.8) |
| Southern Europe | 48 | 39 | (81.3) | 4 | (8.3) |
| South America | 10 | 7 | (70.0) | 0 | (0.0) |
| West Indies | 89 | 59 | (66.3) | 6 | (6.7) |
| Other | 11 | 3 | (27.3) | 1 | (9.1) |
| Total | 994 | 518 | (52.1) | 53 | (5.3) |

tory of blood transfusion, tatoos and jaundice. No detailed travel, sexual or employment history was taken. Sufficient sera remained of 994 subjects (683 females, 311 males) for testing for anti-HAV and anti-HEV. These included all subjects found to be positive for HBsAg and anti-HCV in the previous study.

To establish whether this sample was representative of the population of patients attending general practitioners in the Camberwell health district, we revisited six of the practices which were used in the original study. Current attendance diaries at the practices were examined and data on age and sex of 1,048 patients attending on consecutive days were recorded. Comparison between the current attendees at the practices and the original sample taken showed that the sample was representative in terms of age and sex though the age group 45–64 years was somewhat exaggerated (Table I).

Camberwell is an inner-city area with a large immigrant population. The majority of its inhabitants belong to social classes IIIm, IV and V. Census data for 1991 are available for the areas served by 10 of the 12 practices sampled, which contributed 84% of the total sample. The population served by these practices had 20.6% of adults unemployed, 62.1% of the population in rented local authority housing, and 12.6% of the population living in housing classified as overcrowded. Of the population, 22.8% described themselves as having an ethnic background other than "UK white"; the sample reflected this with 284 subjects (28.6%) born outside the UK (Table II) and 710 born in the UK of whom 588 had parents also both born in the UK.

## Methods

Sera were rapidly separated and stored at −20°C until testing. Anti-HEV IgG was assayed using an enzyme immunoassay (EIA) which employs two recombinant HEV proteins, representing sequences from the open reading frame 2 (ORF2) and ORF3 of a Burmese HEV strain (Abbott Laboratories, Delkenheim, Germany). Anti-HAV total immunoglobulin was tested for using a micro-particle EIA (IMx HAVAB-Abbott). The performance and interpretation of these assays were as stated by the manufacturer. Statistical analysis was carried out using Chi-squared and Fisher's exact tests and by Stepwise logistic regression.

## RESULTS

### Anti-HAV Total Immunoglobulin

Of 994 sera tested, 518 (52.1%) were positive for anti-HAV. Three hundred twenty (45.1%) of 710 of UK born subjects and 198 (69.7%) of 284 non-UK born subjects were positive (Table II). Neither sex was positive in statistically significant excess. Age specific prevalence of anti-HAV is shown in Figure 1. There was some variation in the seroprevalence in UK born subjects when different GP practices were compared. Stepwise logistic regression using age as the determinant variable showed this variation not to be significant. There was no significant association between a history of tattoos and seropositivity in either the UK or non-UK groups. Forty-seven (14.7%) of 320 UK and 4 (2%) of 198 non-UK seropositive subjects gave a history of jaundice. A history of blood transfusion was associated with seropositivity seen in the total (82/518 anti-HAV positive vs. 38/476 anti-HAV negative) and UK born (47/320 anti-HAV positive vs. 33/390 anti-HAV negative) groups. Logistic regression with age as the dependent variable showed a history of blood transfusion and jaundice to be significantly associated with anti-HAV seropositivity. In the UK born population there was a significant association between having

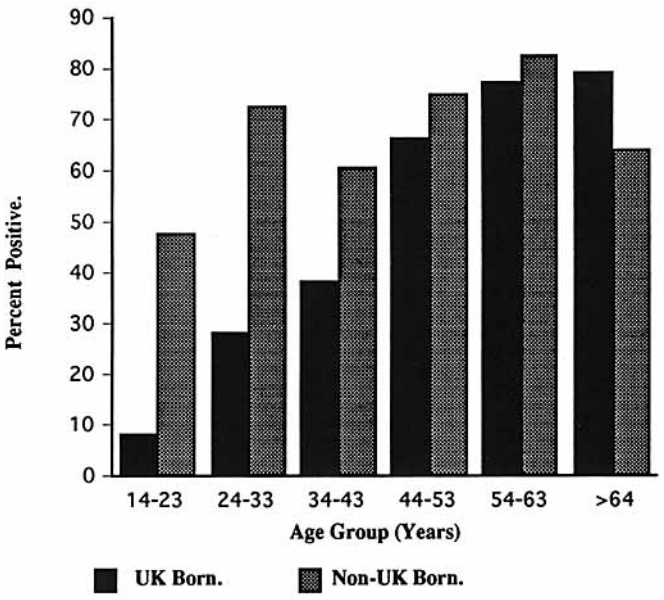


Fig. 1. Age specific prevalence of anti-HAV IgG.

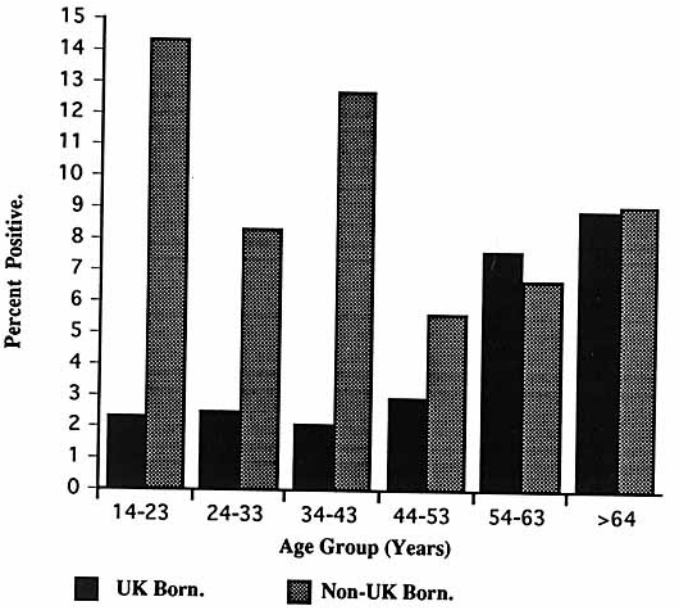


Fig. 2. Age specific prevalence of anti-HEV IgG.

one or more parent born outside the UK and seropositivity (37/122 vs. 283/588 with both parents born in UK, $\chi^2$ 12.9 $P < 0.001$).

### Anti-HEV IgG

Of 994 sera tested, 53 (5.3%) were positive for anti-HEV. Twenty-eight (3.9%) of 710 of UK born subjects and 25 (8.8%) of 284 non-UK born subjects were positive. Neither sex was positive in statistically significant excess. Age specific prevalence is illustrated in Figure 2. There was no significant association between a history of tattoos, blood transfusion, jaundice or individual practices in the sample studied. There was no significant difference between the numbers of UK born subjects seropositive who had neither parent (23/588) or one or more parent (5/122) born outside the UK.

### Interrelationships Between Seropositivity for Hepatitis Viruses

Previous testing of the sample [King et al., 1991] had shown 10 (1%) of 1,002 sera to be positive for HBsAg, while 379 (38%) of 1,002 had other serological markers for HBV exposure (anti-HBc and anti-HBs). Eight (0.8%) of 1,002 sera were positive for anti-HCV. No significant association was found between the presence of anti-HEV or anti-HAV and anti-HBc, anti-HBs or HBsAg, or with the presence of anti-HCV.

## DISCUSSION

Within the sample two patterns of age-specific prevalence of anti-HAV are apparent. In the UK born sample seroprevalence increases gradually with increasing age, reaching a high level in late adulthood, contrasting with that of the non-UK born sample where antibodies are present at the same high prevalence in all age groups; a consequence of infection early in life in the developing world, with antibodies persisting into adulthood. For the UK-born population, infections are likely to occur throughout adolescence and adulthood, and as a consequence their clinical severity increases [Forbes and Williams, 1988]. The very high levels of seroprevalence observed in the oldest age groups of the UK born population in the present study is likely to reflect a cohort effect from a childhood when infection was much more common [Melnick, 1995]. A single survey cannot distinguish between this and a rising incidence with age or the effects of both factors.

There are few epidemiological studies on the seroprevalence of anti-HAV in similar populations in the UK available for comparison; most data on anti-HAV seroprevalence and from blood donors and serum taken for other purposes tested at regional laboratories. These have revealed marked geographical variation in anti-HAV prevalence in the UK and strong effects of socioeconomic factors [Gay et al., 1994; Howell et al., 1993; Scott et al., 1989]. Studies on blood donors attending centres in North London in 1991 [Howell et al., 1993], whom the authors regarded as being predominantly "middle class," showed a pattern similar to that of the UK born group in our study, but with an age related prevalence consistently 10–20% below that of our sample. The limited published data suggest our sample to be taken from an area where HAV infection is relatively common. From the data available on each subject it was, however, impossible to examine whether anti-HAV was more common in subjects of low socioeconomic status.

A recent case-control study [Maguire et al., 1995] examined in detail the factors associated with sporadic HAV infection in the UK. It revealed a significantly increased risk of HAV infection with the presence of

young children or persons with hepatitis or other gastrointestinal illness in the household and with travel abroad, particularly the Indian subcontinent. The association we found between previous blood transfusion and anti-HAV is unexpected as transfusion-associated HAV is very uncommon; studies in the USA demonstrated no cases of HAV infection among 1,533 transfusion recipients [Hollinger et al., 1981], though it has been documented in a number of countries including the UK [Skidmore et al., 1982]. An estimated 1 in 5,000 blood transfusions in the UK are thought to be contaminated with HAV [Gay et al., 1994], a rate at which it is unlikely that infected blood could account for more than a small fraction of the anti-HAV positive subjects in our sample who had received transfusions. A risk of transfusion-associated HAV infection does, however, exist, and may increase since the prevalence of anti-HAV in the UK is falling [Gay et al., 1994]. If this association is real and does not represent a form of recall bias then it is likely that other factors perhaps including the associated hospitalisation and surgical procedures account for this association as hospital outbreaks of HAV infection may be more common [Klein et al., 1984] than infection spread by blood or blood products.

In common with HAV, the majority of infections with HEV seem to have been unapparent; only small proportions of those with anti-HEV or anti-HAV gave a history of jaundice. Insufficient sera prevented extensive testing of the anti-HEV positive samples with supplementary assays; 44 sera were tested for anti-HEV IgM (Abbott Laboratories) and none of these were positive (data not shown). It is therefore unlikely that the symptoms for which the subjects were attending the practices were related to primary HEV infection.

From our study it is impossible to be certain whether the infection of UK-born anti-HEV positive subjects occurred in the UK or abroad as no detailed travel history was taken. However, no significant excess of anti-HEV was found in those subjects who had one or more parents born outside the UK and could be expected to be more likely to travel outside the UK. In contrast anti-HAV was more common in those with non-UK parents, and it is plausible that some of these infections occurred abroad or from secondary spread from infected relatives returning from abroad.

In areas where HEV is endemic, seroprevalence rises in the late teems and early adulthood [Arankalle et al., 1995], at which time the peak incidence of HEV infections is likely to occur. We did not observe this in our UK born sample, suggesting either that infection occurs in an older age group in the UK or more likely that the increased prevalence in later life reflects a cohort of subjects infected in the past when socioeconomic conditions made exposure to the virus more common; a cohort effect similar to that observed with HAV. Our data showed a fall in the prevalence of anti-HEV in non-UK born subjects over 44 years of age; variable persistence of anti-HEV following initial infection has been documented [Khuroo et al., 1991; Goldsmith et al., 1992], and the lower seroprevalence may be the result of the disappearance of anti-HEV in a proportion of subjects in the years following initial infection.

The prevalence of anti-HEV observed in our inner-city sample is higher than that reported in healthy individuals in Italy (0.74%) [Zanetti et al., 1994] and in studies on blood donors in Germany (0%) [Wang et al., 1993] and the Netherlands (1.1%) [Zaaijer et al., 1993]. However, it closely parallels that in a community based study in Turkey [Thomas et al., 1993] where an overall 5.9% seroprevalence was found and where anti-HEV was more common in those of low socioeconomic status. Although the data did not permit the examination of the association of anti-HEV to the socioeconomic status of individuals, the sample was drawn from a deprived population. The pattern of age specific seroprevalence differed from that reported in Turkey, increasing in the fourth decade of life rather than the fifth as we observed, possibly reflecting the relative rates of improvement in sanitary conditions.

The data show a relatively low prevalence of antibodies to HEV in an area where HAV infection is common, and one in which there could be expected to be a risk of imported disease. This may in part be a result of the transitory nature of the anti-HEV antibody response, though the biophysical properties of the HEV virus are more likely to account for this. Relative to HAV, HEV particles are excreted in stools in low numbers during acute infection and remain very labile [Bradley et al., 1993] and hence susceptible to unfavourable environmental conditions and sanitary treatment. Studies [Bradley et al., 1993; Aggarwal and Subash, 1994] have suggested only low rates of secondary spread from infected persons in comparison to HAV and it is likely that epidemics of HEV infection occur only when drinking water is grossly contaminated. Despite the socioeconomic deprivation of the area we sampled, HEV infection and transmission appear uncommon relative to HAV.

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